Visual Search in Progressive Supranuclear Palsy

Daniel T. Smith[1] and Neil Archibald[2]

1. Department of Psychology, Upper Mountjoy, Durham University, Durham, UK.
2. South Tees Hospitals NHS Foundation Trust, The James Cook University Hospital, Middlesbrough, UK

Abstract

Progressive Supranuclear Palsy is often considered as disease of the motor system and is characterised by a profound oculomotor impairment. The oculomotor system is also known to be fundamentally important in cognitive processes such as attention and working memory but the way in which these functions are affected by PSP is not well understood. In this chapter we outline the pathology and typical presentation of PSP, with a focus on the oculomotor impairment, briefly outline the role of the oculomotor system in spatial cognition and discuss some key studies examining spatial attention and memory in PSP. We then present new data from a study that specifically examined the effect of PSP on visual search. Our results demonstrated a profound impairment of visual search which is most severe for feature search along the vertical axis. These findings are interpreted with respect to the biased competition theory of attention and we discuss possible clinical applications of our results.

Acknowledgement

We are very grateful to the members of the Middlesbrough, Durham and Sunderland branches of the PSP Association for their assistance and participation in this study.

Cite as Smith D.T., Archibald N. (2018) Visual Search in Progressive Supranuclear Palsy. In: . Current Topics in Behavioral Neurosciences. Springer, Berlin, Heidelberg

1. Progressive Supranuclear Palsy

Progressive Supranuclear Palsy (PSP), or Steele-Richardson-Olszewski syndrome (Steele, Richardson, & Olszewski, 1964) is a progressive neurodegenerative disorder with a population prevalence of 5–6 cases per 100,000 and an incidence of 1 to 2 per 100,000 per year (Bower, Maraganore, McDonnell, & Rocca, 1997; Nath et al., 2001; Schrag, Ben-Shlomo, & Quinn, 1999). PSP is characterised by progressive gait disturbance, including frequent backward falls, and a vertical gaze palsy. Other clinical features include bradykinesia, axial and limb rigidity, speech and swallowing problems and both cognitive and behavioural changes (Golbe, 2014; Höglinger et al., 2017). There is considerable clinical heterogeneity, however, making diagnosis challenging (Boxer et al., 2017). Post-mortem studies suggest misdiagnosis rates are high, with many patients either incorrectly diagnosed in life, or dying without an explanation for their symptoms (Williams et al., 2005; Yoshida et al., 2017). Patients typically present in their 5^{th}-7^{th} decade and mean survival is 6-9 years (Glasmacher, Leigh, & Saha, 2017).

Although PSP is often described as an "Atypical Parkinsonian" disorder, and may be misdiagnosed as Parkinson's disease (PD), it is a neuropathologically distinct entity. PSP is associated with the deposition of hyperphosphorylated tau as neurofibrillary tangles, neuropil threads, and fibrillary gliosis in the cortex, basal ganglia and brainstem (Dickson, Ahmed, Algom, Tsuboi, & Josephs, 2010). Tau proteins are involved in the development of the microtubules that maintain the structure of cells in the brain. Hyperphosphorylation of tau occurs when the phosphorylation sites become saturated, causing the protein to dissociate from the microtubules. This dissociation results in the destabilization of microtubule, leading to the disruption of signalling between neurons. This disruption is likely to account for the neurological problems experienced by people with PSP. The dissociated tau protein also accumulates into neurofibrillary tangles that disrupt intracellular functions and may contribute to the pathology of PSP. Different patterns of tau distribution may contribute to the clinical variability in presentation and progression. For example, prominent cortical

Cite as Smith D.T., Archibald N. (2018) Visual Search in Progressive Supranuclear Palsy. In: . Current Topics in Behavioral Neurosciences. Springer, Berlin, Heidelberg

pathology may explain the broad range of cognitive impairments seen in PSP, including problems with executive functions (Gerstenecker, Mast, Duff, Ferman, & Litvan, 2013; Robbins et al., 1994), apathy (Brown et al., 2010), impulsivity (Zhang et al., 2016) and social cognition (Ghosh et al., 2012 see Burrell, Hodges and Rowe 2014 for a review). In contrast, the oculomotor problems observed in PSP are more likely to be explained by degeneration of premotor centres in the midbrain and brainstem responsible for the production of eye-movements, rather than the cortical oculomotor network. PSP is characterised by the vertical paralysis of gaze, but as the disease progresses horizontal saccades are also lost, along with other oculomotor behaviours such as vergence (Chen et al., 2010). The vertical ophthalmoplegia is likely caused by degeneration of two key midbrain structures: the medial longitudinal fasciculus (riMLF), which contains the premotor neurons that drive~~s~~ vertical eye-movements, and the interstitial nucleus of Cajal (INC), which controls the maintenance of stable fixation. It seems likely that vertical saccades are lost before horizontal saccades because the riMLF is more rostral than the parapontine reticular formation (which controls horizontal saccades) and succumbs earlier in disease progression (Chen et al., 2010; Steele et al., 1964).

2. Visuospatial Attention

Visuo-spatial attention allows us to select information from task-relevant locations at the expense of signals from irrelevant locations. The focus of attention is often compared to a spotlight on a theatre stage (Posner, 1980), such that the region of space within the spotlight 'illuminated' by attention, and processed preferentially to region outside the spotlight (although in fact attending to a location appears to increase the perceived contrast and improves spatial resolution, rather than enhancing perceived luminance per se (Carrasco, Ling, & Read, 2004; Yeshurun & Carrasco, 1998)). Like a spotlight on a stage, the focus of attention can be moved around the environment, and there are two different mechanisms that control this orienting of attention. Attention can be can be

guided endogenously, in response to the observers goals and desires, or exogenously, in response to salient events in the environment. These two modes of orienting appear somewhat independent of one another. For example, orienting of exogenous attention is rapid but transient, such that attentional facilitation is maximal ~150ms after the onset of a cue but then rapidly decays. In contrast endogenous orienting is relatively slow, reaching its peak ~300ms after cue onset, but sustained (Muller & Rabbitt, 1989) . The exogenous mode of orienting is also involuntary, to the extent that certain types of stimuli, such as sudden onsets, summon attention even when the participant is aware that the target is unlikely to appear at the cued location (Posner, 1980). Endogenous orienting is largely under conscious control. Consistent with the behavioural evidence that these two modes of orienting are dissociable, exogenous and endogenous orienting appear to activate different networks of brain areas (Corbetta & Shulman, 2002)

Both modes of attention are typically associated with an actual movement of the eyes, which brings the location of interest into the fovea. This mode of orienting is often referred to as an overt shift of attention. However, attentional orienting can occur covertly, such that the spotlight of attention is moved around while the eyes remain fixated (Posner, 1978). These exogenous and endogenous modes of attentional facilitation are complemented by an inhibitory mechanism (Inhibition of Return) that biases the visual system away from previously explored parts of a display (Posner, Rafal, Choate, & Vaughan, 1985). This inhibitory effect has a perceptual component, which suppresses visual input from salient parts of the scene and a motor component, which biases the eye-movement system against programming movements towards parts of the scene that have already been gazed at (Hilchey, Klein, & Satel, 2014; Klein, 2000).

At a theoretical level, the cognitive mechanisms mediating visuospatial attention are generally agreed to be tightly coupled to the systems that control eye-movements (Awh, Armstrong, & Moore, 2006), see also Hunt, Reither, Hilchey & Klein (2018). For example, the brain areas involved in saccade control are spatially overlapping with those implicated in spatial attention

(Corbetta et al., 1998; de Haan, Morgan, & Rorden, 2008), and temporary neurodisruption of these brain areas with Transcranial Magnetic Stimulation leads to impairments of both spatial attention and saccade control (Zangemeister, Canavan, & Hoemberg, 1995), attentional orienting (Chambers, Stokes, & Mattingley, 2004; Fierro et al., 2000; Grosbras & Paus, 2002; Smith, Jackson, & Rorden, 2005, 2009b) and visual search (Lane, Smith, Schenk, & Ellison, 2012a, 2012b; Muggleton, Juan, Cowey, & Walsh, 2003). Furthermore, there is a mandatory shift of attention to the goal of a saccadic eye-movement (Shepherd, Findlay, & Hockey, 1986), even when the observer knows a target is more likely to appear at a different location (Deubel & Schneider, 1996), and there are several examples of neuropsychological associations between impaired oculomotor function and disrupted covert orienting of attention (Craighero, Carta, & Fadiga, 2001; Gabay, Henik, & Gradstein, 2010; Smith, Jackson, & Rorden, 2009a; Smith, Rorden, & Jackson, 2004; Smith & Schenk, 2012). The tight coupling between oculomotor control and spatial attention can also be observed in healthy participants whose eye-movements have been experimentally constrained. These participants show a deficit of covert attention in regions of space that cannot be reached with a saccadic eye-movement (Craighero, Nascimben, & Fadiga, 2004; Morgan, Ball, & Smith, 2014; Smith, Ball, & Ellison, 2014; Smith, Ball, Ellison, & Schenk, 2010; Smith, Rorden, & Schenk, 2012), which is particularly severe for exogenous orienting. Given that PSP is associated with a profound oculomotor impairment, and oculomotor impairments are associated with deficits of covert attention (Smith & Schenk, 2012), it seems reasonable to predict that people with PSP will have a deficit of covert attention, and this deficit will be more severe for tasks that engage exogenous attention.

Consistent with this idea, Rafal and colleagues conducted a series of experiments using Posner's cueing task (1980) to examine the extent to which the vertical paralysis of gaze affected orienting of attention in PSP (Posner, Cohen, & Rafal, 1982; Posner et al., 1985; Rafal, Posner, Friedman, Inhoff, & Bernstein, 1988). Exogenous orienting was assessed by presenting a cue in the periphery which, after a variable delay (10,150,350,550ms) was followed by a target. This target

appeared at the cued location on 50% of trials, thus removing the incentive for participants to voluntarily attend to the cued location. Critically, on half the trials stimuli appeared along the horizontal axis, and on the other half they were aligned vertically. In healthy participants one typically observes faster reaction times at the cued location, but only when the delay between cue and target onset is short (<150ms). In contrast, when the delay is longer than ~300ms, reactions times to targets at the cued location are slowed by IOR (Posner & Cohen, 1984). This is exactly the result observed by Rafal et al., (1988) in a group of patients with Parkinson's Disease (PD), and the pattern was the same for horizontally and vertically presented arrays. In contrast, patients with PSP showed a very marked horizontal/vertical asymmetry. Specifically, the facilitatory effect of peripheral cues appearing along the vertical axis was significantly weaker than those along the horizontal axis, and was delayed until 350ms. Furthermore, patients with PSP did not present the normal IOR effect at longer cue-target delays when stimuli were presented along the vertical axis, whereas IOR was normal along the horizontal axis (Posner et al., 1985). Endogenous orienting was assessed using an arrow cueing task, in which a centrally presented arrow correctly indicated the location of the upcoming target on 80% of trials. In this task the cues elicited endogenous shifts of attention that had a similar time-course irrespective of the axis along which attention was oriented, although the benefit was slightly smaller along the vertical axis. Rafal et al., conclude that PSP is associated with deficits of visuospatial attention, and link these deficits to the ophthalmoplegia.

These data seem to suggest that people with PSP have a deficit of exogenous, covert attention that is specific to the vertical axis and is not present in PD. It is plausible to interpret this deficit of exogenous orienting as a potentially unique, cognitive marker that can differentiate PSP from PD. Given the issues surrounding the problems of differentiating between PSP and PD, particularly early in disease progression, a specific cognitive marker for PSP might have important practical applications for the early and accurate diagnosis of PSP. However, we believe this interpretation may be somewhat premature, as there are several reasons to be cautious when

interpreting the data from these studies. Firstly the delay between cue and target onset was short the cue and target overlapped, such that the target was superimposed on the cue whereas at longer cue-target onset asynchronies (CTOAs) the target appeared on the background. Thus, there were differences in the visibility of the target at cued and uncued locations at short CTOAs which might account for some of the effects. Secondly, PSP is associated with akinesia which makes the interpretation of raw RT, which depends on the initiation of a button press, rather problematic. Unfortunately the study by Rafal makes no mention of the variance of the RT data in their sample, but the very high RT cut-off (3500ms) suggests a considerable variation in response times. Finally, using an arrow cueing task is not optimal for studying endogenous orienting because arrow cues are known to engage both endogenous and exogenous attentional processes (e.g. Ristic, Friesen, & Kingstone, 2002; Tipples, 2002), so cannot be considered a 'pure' measure of endogenous orienting.

An alternative approach to examining visuo-spatial attention in PSP is to use a visual search task rather than the Posner cueing task. Visual search requires participants to detect the presence or absence of a target item amongst distracters. Varying parameters such as the salience of the target and the number of distracters allows the measurement of search efficiency, which refers to the amount of change in reaction time caused by adding additional distracter items(J.M. Wolfe, 2003). When the target of the search is defined by a single, salient feature such as orientation or colour, search can be highly efficient, such that the target seems to 'pop-out' and additional distractors have a negligible effect on search time (<10 ms per additional item). This type of search engages more reflexive exogenous attentional processes. In contrast, when the target is non-salient or characterised by a conjunction of features participants must engage more endogenous, effortful attentional processes to search through each item in a serial fashion until they detect the target (J.M Wolfe, 1998). This type of search is inefficient, such that additional distractor items have a substantial effect on search time (>30ms/item).

There are several other advantages to using search tasks over cueing tasks to measure attention in PSP. Firstly, it is easier for patients to understand the task as there is a single visual event for them to detect (the target), and they do not have to worry about accidentally responding to cues. Secondly, because there is no salient pre-cue, the effects of covert attention are unlikely to be confounded with the effects of IOR. Thirdly, by examining both the overall RTs and search efficiency it may be possible to partly control for the high levels of variance in RT. Fourthly, visual search tasks are known to be sensitive to disruptions to the oculomotor system in healthy participants, such that feature search is impaired when targets appear at locations that cannot become the goal of a saccadic eye-movement, whereas conjunction search is unaffected (Smith et al., 2014; Smith et al., 2010). In contrast, the effect of disrupting the oculomotor system on cueing tasks is less consistent, with some authors reporting disruption to exogenous orienting but preserved endogenous orienting, social attention and perceptual IOR (Morgan et al., 2014; Smith et al., 2012), others arguing for disrupted endogenous orienting (Craighero et al., 2004) and a recent report of disrupted perceptual IOR (Michalczyk, Paszulewicz, Bielas, & Wolski, 2018). Finally, visual search tasks are closer to the 'real-world' than cueing tasks so offer a somewhat more ecologically valid measure of visuospatial attention than cueing tasks.

Several studies have examined visual search in PSP, typically as part of a larger battery of neuropsychological tests. These studies suggest that visual search is indeed impaired in PSP compared to PD. For example, Kimura, Barnett, and Burkhart (1981) presented 20 line drawings of familiar objects on a vertical surface and examined how long it took for patients to locate a target picture. Patients with PSP were significantly slower than patients with PD, patients with frontal lesions and patients with occipital lesions. This last result is notable, given that patients with occipital lesions are likely to suffer some form of cortical blindness so might be expected to struggle with visual search tasks (e.g. Lane, Smith, Ellison and Schenk 2010). Two other studies also report that people with PSP perform worse than PD patients on the Visual Search Test (Monza, Soliveri,

Radice, & et al., 1998; Soliveri et al., 2000). However, these latter two studies are hard to interpret in terms of visuospatial attention, as the Visual Search Test used by Monza et al., actually measures the ability to name pictures of objects, rather than the ability to locate a target stimulus among distractors. Furthermore, the description of the impairment is rather incomplete. Specifically, the tasks all require patients to identify complex drawings of objects, which is likely to engage endogenous attentional processes, but none of the studies explicitly examined feature search in PSP. The extent to which feature search is also disrupted in PSP therefore remains unknown. Neither do the studies report performance on target-absent trials, which is an important indicator of participants' ability to correctly terminate a search in the absence of a target. Furthermore, none of the studies varied set size, making it impossible to know whether PSP impairs only the speed of search, or whether it also affects the efficiency of the search. With respect to the impact of ophthalmoplegia on visuospatial attention, unlike the cueing task of Rafal et al., these studies did not directly compare search times for targets on the horizontal and vertical axis. So, although previous studies offer some evidence that visual search is relatively impaired in PSP, they do not offer a very complete characterisation of the visual search impairment, nor do they speak to the theoretical claim that the attentional impairment in PSP is linked to the oculomotor impairment. The work described in the next section attempts to address some of the issues by examining visual search in groups of patients with PSP.

3. Methods

Participants

Seventeen participants with Progressive Supranuclear Palsy (PSP) were approached via the Movement Disorder Service at The James Cook University Hospital, Middlesbrough. Twelve agreed to participate (6 male aged 63-80, mean age 71) and seven with PD (age 64-69, mean 66). All participants with PSP met the National Institute of Neurological Disorders and Stroke and Society for

PSP, Inc. (NINDS-SPSP) (Litvan et al., 2003) criteria for clinically probable or definite PSP. The study was approved by the North East - Newcastle & North Tyneside 1 Research Ethics Committee (15/NE/0254) and Durham University Department of Psychology Research Ethics Committee.

Stimuli & Apparatus

The experimental stimuli were generated using a Cambridge Research Systems ViSaGe graphics card and displayed on a 17-inch Sony Trinitron CRT monitor with a refresh rate of 100Hz. Responses were collected using a two-button button-box. Saccadometry was performed using a BioPac 150 recording EOG at 500 Hz. The visual search target was a blue 'c' shape oriented at 45°. In the Feature search task the all distractor items were also blue 'c's, oriented at 215°. In the Conjunction search task distractors could also be ether blue 'c's, oriented at 215° or yellow 'c's, oriented at 45° (see Figure 1). Array items were presented at 10° from the centre of the screen on a black background. In 4-item arrays the stimuli appeared on the cardinal compass directions (N, E, S, W). In 8-item arrays stimuli appeared at cardinal directions and intermediate points (N, NE, E, SE, S, SW, W, NW). Participants sat 50cm from the display with the head supported by a chinrest.

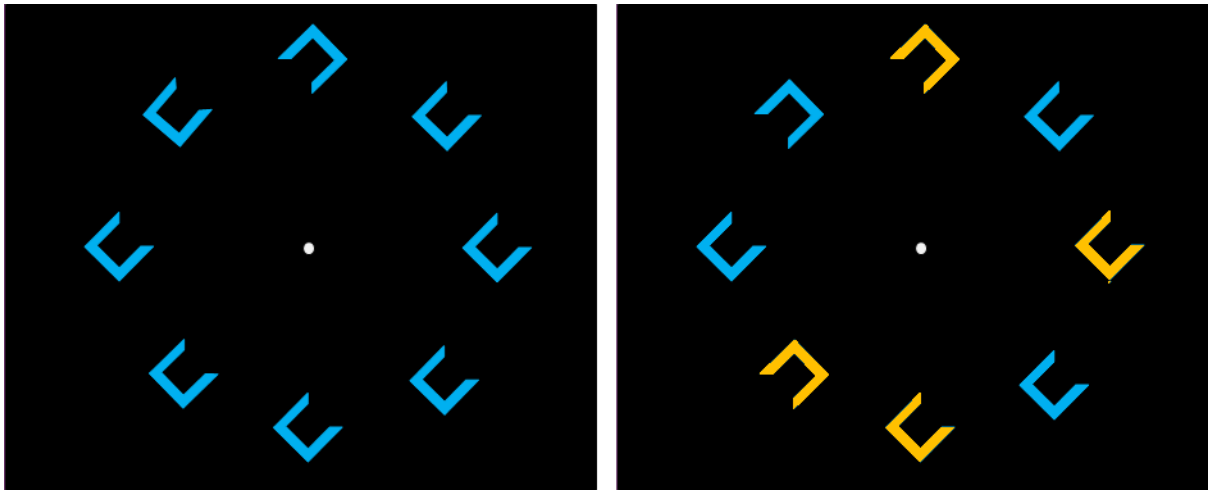

Fig 1 Examples of eight item visual search arrays. The left panel shows the feature search and the right the conjunction search.

Procedure

Eight participants with PSP completed a saccadometric test to establish the extent of their ocular motility. In this test participants were presented with a black spot at fixation. After 2000ms the spot jumped into the periphery. Participants were instructed to follow the spot with their eyes and press a button when they were fixating it. Following the button press the spot returned to the centre and the next trial began. Each run consisted of 10 jumps that increased in magnitude in 1° steps, starting with a 1.5° jump. Participants completed 4 runs (Centre-Up, Centre-Left, Centre-Down, Centre-Right).

Following the saccadometry patients completed the visual search tasks. All AMC and seven patients with PSP completed both tasks. Two patients with PSP completed the Feature search task but not the Conjunction search task and three patients with PSP completed the Conjunction but not the Feature search tasks. Thus 8 patients completed the Feature search task and 9 patients completed the Conjunction search task. Both tasks began with the appearance of a fixation point for 1000ms, followed by the appearance of a search array comprising 4 or 8 items. This array remained presented until a response was made. Participants were instructed to press one button when a target was present, and the other the target was absent. They were also instructed fixate the centre of the array and try not to make eye-movements. There was a 2:1 ratio of 8 item arrays to 4-item arrays and a 2:1 ratio of target present to target absent trials. On target present trials the target appeared at each location in the array with equal probability. All participants completed one block of 36 practice trials and two blocks of 108 experimental trials.

4. Results

Saccadometry

All PSP patients presented with supranuclear ophthalmoplegia that was more severe for vertical than horizontal saccadic eye-movements (this is a key diagnostic criteria for PSP and was established during clinical examination by a neurologist). The extent of the ophthalmoplegia was more formally assessed with saccadometry in 8/12 PSP patients. Vertical saccadic eye-movements were absent in all participants with PSP. Horizontal eye-movements were present in all patients. Table 1 shows the oculomotor ranges of the 8 participants for whom saccadometric data were available. The maximum amplitude of leftwards saccades was significantly reduced compared to that of rightwards saccades than (8.2° vs 9.6°; $t_{(12)} = 3.42$, $p < .01$). The main sequence for horizontal saccades was also somewhat impaired in the PSP group, but was similar for left and rightwards saccades (Chen et al., 2010)

		Max Amplitude				**Main Seq**		
ID	**Group**	**Left**	**Right**	**Up**	**Down**	**Left**	**Right**	**Meds**
1	PSP	11.5	11.5	0	0	0.16	0.1	-
2	PSP	6.8	7.8	0	0	0.73	0.5	L
3	PSP	7	8	0	0	0.70	0.89	-
4	PSP	8.8	9.9	3	0	0.68	0.34	-
5	PSP	6.3	8.9	0	0	0.38	0.64	A
6	PSP	7.5	11	0	0	0.8	0.84	L
7	PSP	10.1	10.5	0	0	0.3	0.6	D, L
8	PSP	7.5	9	0	0	0.5	0.85	-
Mean		*8.2*	*9.6*			*0.53*	*0.59*	

Table 1 Saccadometry results. The oculomotor range was defined as the point at which participants ceased to scale their eye-movements with increasing target eccentricity. The main sequence describes the correlation coefficient (Pearsons R) between saccade amplitude and peak velocity. Meds: A= Amantadine, D= Donepezil, L= Levodopa

Feature Search

One patient in the PSP group had a median reaction time of >10s, so was excluded from the analysis. The remaining data were filtered to remove anticipations (<1%), incorrect responses (6% PSP), trials where the target appeared on at one of the intercardinal compass points (i.e. NE, SE, SW, NW) and Target Absent trials. At each set size we collapsed trials where the probe appeared the N and S positions into a 'Vertical' condition, and trials where the probe appeared the E and W positions into a 'Horizontal' condition.

The median reaction times for Target Present trials were subjected to a 2 x 2 x 3 factor ANOVA with within-subjects factors of Set Size (4, 8) and TargetAxis (horizontal, vertical) and a between-subjects factor of Group (PSP, AMC). We observed a significant 2-way interaction between Group and TargetAxis ($F_{(1,14)} = 5.28$, $P < 0.05$, $\acute{\eta}2 = .27$). Inspection of Figure 2 (top row) suggests that this effect was driven by an increase in reaction time for targets appearing on the vertical axis that was specific to the PSP group. This impression was confirmed with a t-test ($t_{(7)} = 2.56$, $p = .038$). Overall the PSP group was significantly slower than the AMC group, (2951ms vs 936ms; $F_{(1,14)} = 10.75$, $P < .01$, $\acute{\eta}2 = .26$).

We also examined the response accuracy using ANOVA. The two groups had similar overall accuracy levels (94% for both groups), and there were no significant main effects of Set Size or Group and no interactions.

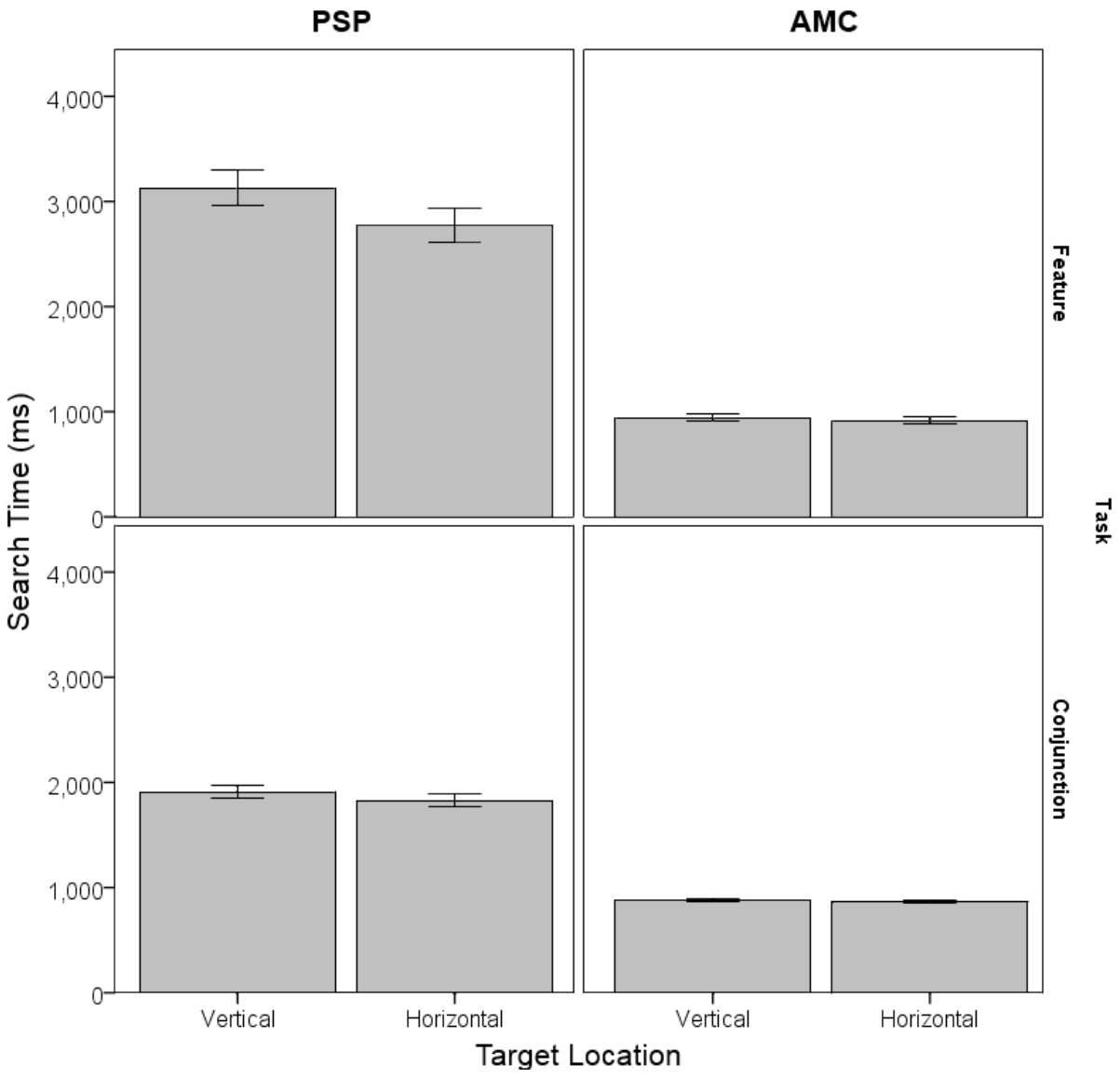

Fig 2 Feature (upper row) and Conjunction (lower row) Search times on Target Present trials in the PSP and Age Matched Control groups. Error bars show 95% within subject confidence intervals (Cousineau 2005)

Figure 3 shows Feature Search times when no target was present. There was a main effect of Set Size, such that both groups were slower on the 8 item than the 4 item arrays $F_{(1,14)} = 4.91$, P = .044, ή2= .26). However, there was no interaction between Set Size and Group $F_{(1,14)} = 1.99$, P = .18, ή2 = .12). As with the target-present trials, there was a main effect of group, such that PSP group

were slower to respond than AMC group (3225ms vs 1036ms; $F_{(1,14)} = 6.81$, $P = .021$, $\eta 2 = .33$). Accuracy on target-absent trials was also examined with a 2 (Set Size) x 2 (Group) ANOVA. The analysis revealed a significant interaction, such that the PSP group tended to produce more false positives as the array size increased from 4 to 8, whereas the AMC group produced fewer false positives as the set size increased (Figure 3).

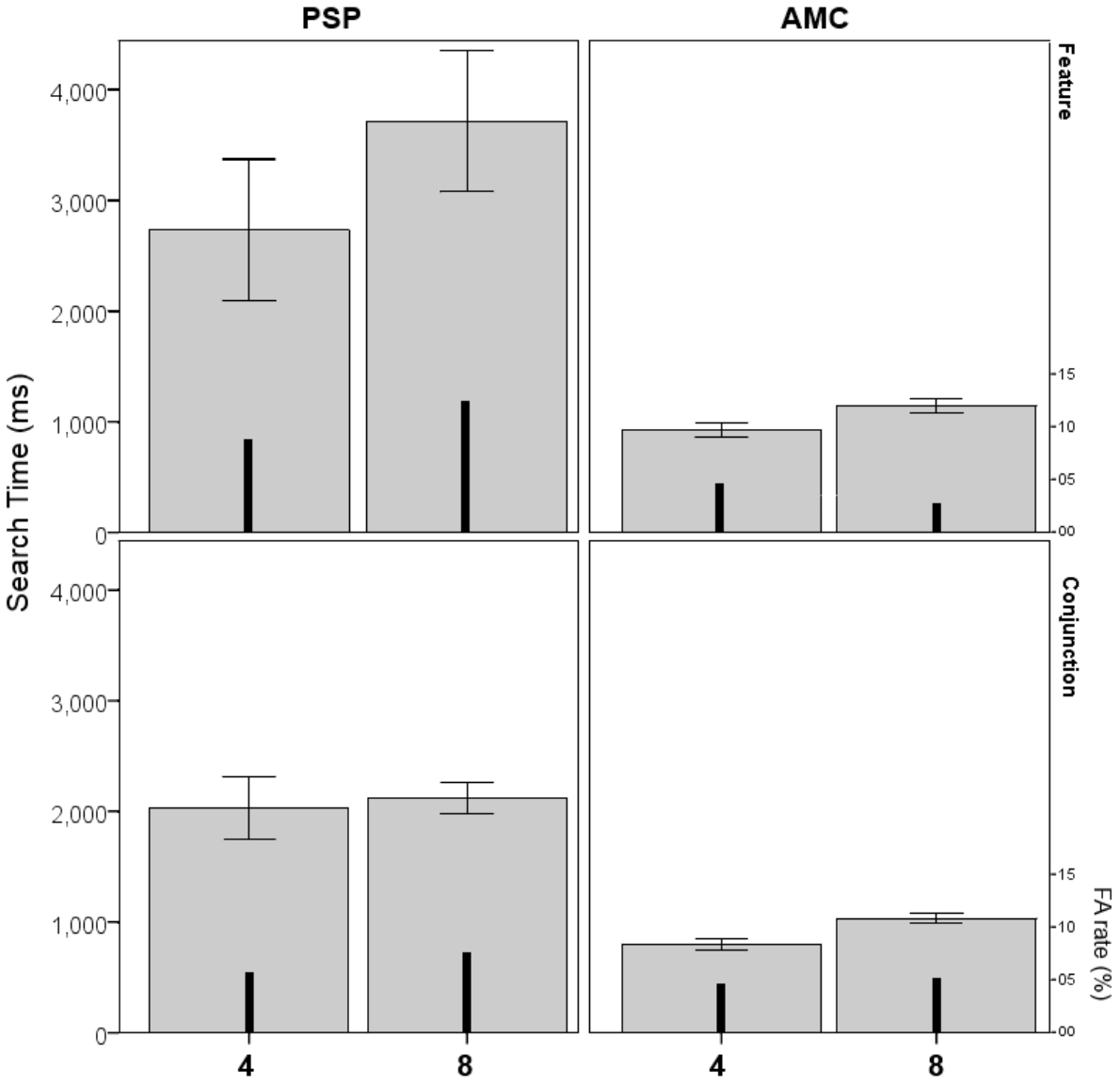

Fig 3 Mean RTs on Target Absent trials at each set size. Solid black bars show False Alarm rates (%). Error Bars show 95% within-subject confidence intervals.

Conjunction Search

The pattern of data in Conjunction Search was rather different to that in the Feature search task (see Figure 2 left column). Firstly, there was a significant main effect of Set Size, such that search was slower when there were 8 rather than 4 items in the search array ($F_{(1,15)}$ = 18.01, P < .01, ή2 = .55). Secondly, there was no interaction between Target Axis and Group ($F_{(1,15)}$ =1 .39, P = .26, ή2 = .09). However, there was a main effect of Group ($F_{(1,15)}$ = 13.37, P < 0.1, ή2 = .48), such that the PSP group were slower than the AMC group (1870 ms vs 873ms). The response accuracy was examined using ANOVA. As with in the Feature search, accuracy was similar in both groups (PSP 96% correct, AMC 97% correct) and there were no significant main effects or interactions.

Figure 3 (bottom row) shows conjunction search performance on Target Absent trials. There was no main effect of Set Size ($F_{(1,15)}$ = 3.84, P = .07, ή2 = .20) and no interaction between Set Size and Group $F_{(1,12)}$ =1.16, P = .229, ή2 = .07) but there was a main effect of Group ($F_{(1,12)}$ = 5.55, P = .033, ή2 = .27), such that such that the PSP group were slower than the AMC group (2092 ms vs 916 ms). The false alarm rate was also analysed, but there were no main effect or interactions.

Search Efficiency

Search slopes were calculated by subtracting the median search time for 4-item arrays from the median search time in 8 item arrays, then dividing the result by 4 (the difference in the number of items in the arrays). A slope of 0ms/item is indicative of entirely parallel search, a slope greater than 0 indicates an increasingly serial search [Wolfe 2003]. In the AMC group the Feature slopes were clustered around 0 with a mean of 30 ms/item, which did not significantly differ from 0 ($t_{(7)}$= 1.33, p= .22, 95% CI [-23, 85]). Conjunction search slopes were all positive with a mean of 91 ms/item, which was significantly different to 0 ($t_{(6)}$= 8.63, p < .01, 95% CI [66, 116]). In the PSP group Feature the mean slope was 312 ms/item ($t_{(7)}$= 1.5, p= .18, 95% CI [-180, 806]). However, this result

is difficult to interpret due to the large heterogeneity in the slopes. Conjunction search slopes for the PSP group were all above zero, with a mean of 203 ms/item ($t_{(8)}$= 3.2, p= .014, 95% CI [54, 351]).

5. Discussion

To briefly summarize these results, the PSP group was significantly slower than the AMC group on target-present and target absent trials on both search tasks. Furthermore, patients with PSP showed an impairment of feature search along the vertical axis compared to the horizontal axis, but there was no vertical impairment during conjunction search. In contrast, search times of age matched controls were not affected by the location of the target. Accuracy of target detection was similar in the PSP and AMC groups. However, increasing set size during feature search led to more false alarms in the PSP group but fewer false alarms in the AMC group

The finding that patients with PSP are significantly slower that age-matched control on both feature and conjunction search tasks indicates the presence of a problem with and is consistent with previous reports the PSP impairs visual search in complex scenes (Kimura et al., 1981). However, we have extended the previous findings by demonstrating that very simple feature search tasks are also slowed in PSP. This is an important result because Feature search tasks engage relatively rapid, automatic attentional process that do not require a serial search through the scene. The fact that PSP disrupts feature search indicates that PSP interferes with the earliest stages of visual selection, and that the visual search impairment observed in PSP is not simply due to an inability to effectively explore the scene with eye-movements. Furthermore, it was also found that patients with PSP were slower than age matched controls to correctly reject no-target trials during the Feature Search task, and more likely to report false positives as set size increased. In contrast, the AMC group became slightly slower but more accurate. The two groups therefore appear to have adopted different speed-accuracy trade-offs in response to increasing task difficulty, with the PSP group becoming less efficient as task difficulty increased. It is not entirely clear what causes this slowing, but one possibility is that the impaired search processes on target-present trials means that patients become

very conservative on target absent trials, perhaps even engaging in a very slow and effortful serial search through all the items to be sure that no target is present (Chun & Wolfe, 1996), or that they engaged in more guessing than the AMC group

Overall our findings are in agreement with previous observations by Rafal et al., (1989) and Posner et al. (1982) of impaired exogenous attentional orienting to peripheral cues presented along the vertical axis. These data appear to offer confirmation that a fully functioning oculomotor system is required for normal exogenous orienting (Jackson et al., 2005; Smith et al., 2004). Furthermore, because PSP affects eye-movements very close to the output end of processing, it is tempting to conclude that the ability to make overt eye-movements is *necessary* to observe exogenous orienting. Such a conclusion would certainly be consistent with neuropsychological evidence that defective saccade execution caused by problems with the extraocular muscles is associated with impaired exogenous attention (Gabay et al., 2010; Smith et al., 2004).

On first inspection the observation of impaired attention along the vertical axis appears broadly in line with the Premotor Theory of Attention (Rizzolatti, Riggio, & Sheliga, 1994), which argues that covert attention depends upon the intention to make a saccadic eye-movement. In this view, both endogenous and exogenous attention depend on the selection of a saccade goal by the cortical and subcortical centres responsible for eye-movements, principally the Frontal Eye Field (FEF), Lateral Intraparietal Area (LIP) and Superior Colliculus (SC) (Fecteau & Munoz, 2006; Schall & Cohen, 2011). Indeed, there is a great weight of neurophysiological evidence that these areas are active during both saccade programming and covert orienting (Corbetta et al., 1998; de Haan et al., 2008; Nobre, Gitelman, Dias, & Mesulam, 2000), and damage to these areas causes problems with eye-movements, covert orienting and visual search (Lane et al., 2012b; Muggleton et al., 2003; Smith & Schenk, 2012). However, on closer examination the interpretation is not quite so straightforward. The first potential problem with interpreting the results in terms of Premotor Theory is that the core oculomotor deficit in PSP is in the riMLF, a premotor structure in the brainstem that drives vertical

eye-movements (Chen et al., 2010; Steele et al., 1964). Given that riMLF does not have any feedback connections to central oculomotor structures (Sparks & Mays, 1990) and is unlikely to be involved in the planning of a saccade, it isn't entirely clear by what mechanism damage to riMLF could disrupt saccade *programming*. Secondly, Premotor Theory predicts that an oculomotor impairment should be associated with deficits in both exogenous and endogenous orienting, but the PSP group were not slower to detect targets on the vertical compared to horizontal axis on the Conjunction search task. This latter finding is hard to reconcile with the notion of a strict coupling between endogenous orienting and the oculomotor system posited by Premotor Theory.

The first problem may be resolved if one considers that the direct, feedforward connections between SC and riMLF leave SC vulnerable to retrograde transneuronal degeneration (Dinkin, 2017; Pinching & Powell, 1971), which describes a loss of presynaptic neurons as a consequence of loss of trophic support from the post-synaptic cells. This degeneration has been observed in other parts of the visual system, notably in the degeneration of the optic tract and LGN following lesions to striate cortex (Cowey, Alexander, & Stoerig, 2011; Kisvarday, Cowey, Stoerig, & Somogyi, 1991). If the loss of cells in riMLF leads to transneuronal degeneration in the SC, this damage would be greater for the parts of the SC that code eye-movements with a more vertical component. This damage would have a profound impact on the ability of the patient to programme vertical eye-movements, and thus potentially to orient attention in vertical space. In this way, transneuronal degeneration could explain the problems patients with PSP experience with feature search. However, resolution of the first problem still leaves the question of why there is no difference between horizontal and vertical target detection during Conjunction in PSP, an issue which may only be resolved by appealing to an alternative theoretical framework, that of Biased Competition.

The core idea of Biased Competition is that signals relating to stimulus salience (e.g. their brightness, size, contrast, orientation) compete with each other in a topographic map of space, called a salience map, in a winner-takes-all competition (Desimone, 1998). The signal that wins the

competition can be read-out by the visual system to guide a shift of attention, or by the oculomotor system to guide a saccade eye movement. The oculomotor signals are self-reinforcing, such that activation in the oculomotor system is fed back into the salience map, thus further biasing activity in favour of the activated location (Bisley, Mirpour, Arcizet, & Ong, 2011). Competition in the salience map is also influenced by the current goals of the observer, such that the locations of stimuli that possess a feature known to be relevant to the current task are also prioritized. In this way the observer can bias the competition towards the stimuli that are most likely to be behaviourally relevant (J.M. Wolfe, 1994). At a conceptual level, Fecteau and others have argued that because this Biased Competition relies on integrating low-level stimulus salience with top-down modulations, the map that represents the competition should be referred to a as a Priority Map, rather than a salience map (Fecteau & Munoz, 2006). Bisley and colleagues have convincingly argued that the Priority Map is instantiated in LIP (Bisley & Goldberg, 2010; Goldberg, Bisley, Powell, Gottlieb, & Kusunoki, 2002), as neural activation in this area correlates with both the onset of saccadic eye-movements, and the covert selection of targets during visual search (Thomas & Pare, 2007). This region has reciprocal connections with early visual areas, which allows for the modulation of visual signals that characterises visuospatial attention (e.g. Hillyard, Vogel, & Luck, 1998; Luck, Chelazzi, Hillyard, & Desimone, 1997), and with key oculomotor centres such as the Frontal Eye Field, which is critical for the generation of endogenous orienting signals, and the Superior Colliculus, which integrates visual and motor signals from cortical and subcortical pathways to specify a saccade goal (Munoz & Everling, 2004; White & Munoz, 2011). LIP therefore seems ideally placed to integrate signals from across a network of brain areas into a single Priority Map.

For simple tasks where one item is highly salient (e.g. in a feature search task) the competitive interactions in the priority map converge to select a single location, which is then powerfully reinforced by the re-entrant activation from the oculomotor system (Barash, Bracewell, Fogassi, Gnadt, & Andersen, 1991). This feedback loop allows the visual system to very rapidly select

the location of the unique feature, irrespective of the number of distractors, which is the signature of efficient visual search (Wolfe, 1998). This selection is driven by bottom-up factors, is largely automatic and corresponds to Posners 'exogenous' mode of attention. A lesion to the oculomotor system that prevented it from reinforcing activation in the Priority map would have the effect of slowing down the selection of the salient location, but not abolishing it completely. This would manifest as impaired feature search when targets appeared at locations that could not be represented in the oculomotor system, exactly as we observed in the PSP group (see also Smith et al., 2014). For search tasks where the target has relatively low salience, as was the case in our conjunction search, there may be multiple peaks of activation in the priority map and the competition between the signals takes time to resolve. This in turn reduces the capacity for the oculomotor system to influence the competition, as the reinforcing signal from the oculomotor system is distributed across multiple locations. Instead, the competition is resolved by top-down processes that reflect to the observers strategic and conscious decisions about which potential target locations should be selected. These processes correspond to Posners 'endogenous' mode of orienting. Thus, a lesion that disrupts oculomotor selection but spares top-down processes, such as the lesion that affects people with PSP, should not affect search that relies primarily on endogenous attentional processes. Consistent with this prediction we have previously shown that disrupting the oculomotor system does not impair conjunction search (Smith et al., 2014) or covert orienting to symbolic cues (Morgan et al., 2014; Smith et al., 2004; Smith et al., 2012). This interpretation also complements other evidence that disruption of the oculomotor system is associated with impaired spatial working memory in PSP (Smith & Archibald, 2018) and healthy participants (Ball, Pearson, & Smith, 2013; Pearson, Ball, & Smith, 2014), as spatial working memory and spatial attention are hypothesised to rely on the same Priority map (Ikkai & Curtis, 2011). Overall the data from our PSP patients fits with a model of an attention system in which orienting of attention is realised via a process of Biased Competition in a Priority Map. Activation in the oculomotor system provides an

input that biases this competition towards the saccade goal, but this bias may not necessarily be sufficient to orient attention to the saccade goal. This conclusion is contrary to the central predictions of Premotor Theory, and adds to the growing body of evidence that Premotor Theory does not offer an adequate account of the relationship between attention and oculomotor control.

The observation that the deficit in exogenous spatial attention in PSP observed by Rafal et al., (1989) generalises to a feature visual search task may also have clinical value. An important issue in clinical practice is the diagnosis of PSP, which is often misdiagnosed as Parkinson's disease. This is problematic because, although superficially PSP and PD often appear to be similar, the underlying pathology is very different. Misdiagnosis is upsetting for the patient and, because many patients with PSP have a poor response to standard treatments for Parkinson's disease, may lead to the use of inappropriate or ineffective treatments. If PSP can be differentiated from PSP using simple cognitive tasks such as visual search, there seems to be the possibility of developing a cost effective tool that would make it easier to ensure that patent with PSP are correctly diagnosed at an early stage of the disease. With the advent of anti-tau immunotherapies as potential disease-modifying agents, earlier and more accurate clinical diagnosis will become increasingly important (Sigurdsson 2016).These data may also help patients and carers better understand the cognitive effects of PSP. Specifically, spatial attention permits the efficient selection of task relevant information from the environment. When these processes go wrong it becomes much more effortful for the patient to select relevant information in the environment. As a consequence, patients may find it harder to find everyday objects such as glasses, books and mugs etc, particularly in cluttered environments and may also become more distractible as they find it hard to ignore irrelevant objects. Better understanding of the cognitive impacts of PSP may help patients and carers develop more effective strategies for coping with PSP.

To summarize, we set out to replicate and extend Rafal et al's., claim that covert spatial attention is disrupted in PSP. We examined feature and conjunction search in patients with PSP and

compared their performance to that of age-matched controls. Consistent with the results of Rafal et al., our patients with PSP had an impairment of feature search that was particularly severe when targets appeared along the vertical axis, and not observed during conjunction search. The visual search of age matched controls was not affected by the location of the target. We argue that that PSP interferes with the ability of the oculomotor system to contribute to competitive interactions in the priority map, thus reducing the efficacy of feature search. From a theoretical perspective the results are consistent with our weak 'exogenous only' version of Premotor Theory (Smith & Schenk 2012), and from a clinical standpoint these findings may have relevance for developing new tools to assist with the early diagnosis of PSP.

6. References

Awh, E., Armstrong, K. M., & Moore, T. (2006). Visual and oculomotor selection: links, causes and implications for spatial attention. *Trends in Cognitive Sciences, 10*(3), 124-130. doi: 10.1016/j.tics.2006.01.001

Ball, K., Pearson, D. G., & Smith, D. T. (2013). Oculomotor involvement in spatial working memory is task-specific. *Cognition, 129*(2), 439-446. doi: 10.1016/j.cognition.2013.08.006

Barash, S., Bracewell, R. M., Fogassi, L., Gnadt, J. W., & Andersen, R. A. (1991). Saccade-related activity in the lateral intraparietal area. I. Temporal properties; comparison with area 7a. *J Neurophysiol, 66*(3), 1095-1108. doi: 10.1152/jn.1991.66.3.1095

Bisley, J. W., & Goldberg, M. E. (2010). Attention, Intention, and Priority in the Parietal Lobe *Annual Review of Neuroscience, Vol 33* (Vol. 33, pp. 1-21). Palo Alto: Annual Reviews.

Bisley, J. W., Mirpour, K., Arcizet, F., & Ong, W. S. (2011). The role of the lateral intraparietal area in orienting attention and its implications for visual search. *European Journal of Neuroscience, 33*(11), 1982-1990. doi: 10.1111/j.1460-9568.2011.07700.x

Bower, J. H., Maraganore, D. M., McDonnell, S. K., & Rocca, W. A. (1997). Incidence of progressive supranuclear palsy and multiple system atrophy in Olmsted County, Minnesota, 1976 to 1990. *Neurology, 49*(5), 1284-1288.

Boxer, A. L., Yu, J. T., Golbe, L. I., Litvan, I., Lang, A. E., & Hoglinger, G. U. (2017). Advances in progressive supranuclear palsy: new diagnostic criteria, biomarkers, and therapeutic approaches. *Lancet Neurol, 16*(7), 552-563. doi: 10.1016/s1474-4422(17)30157-6

Brown, R. G., Lacomblez, L., Landwehrmeyer, B. G., Bak, T., Uttner, I., Dubois, B., . . . Leigh, N. P. (2010). Cognitive impairment in patients with multiple system atrophy and progressive supranuclear palsy. *Brain, 133*(Pt 8), 2382-2393. doi: 10.1093/brain/awq158

Burrell, J. R., Hodges, J. R., & Rowe, J. B. (2014). Cognition in corticobasal syndrome and progressive supranuclear palsy: A review. *Movement Disorders, 29(5)*, 684-693. doi: 10.1002/mds.25872

Carrasco, M., Ling, S., & Read, S. (2004). Attention alters appearance. *Nature Neuroscience, 7*(3), 308-313.

Chambers, C. D., Stokes, M. G., & Mattingley, J. B. (2004). Modality-specific control of strategic spatial attention in parietal cortex. *Neuron, 44*(6), 925-930. doi: 10.1016/j.neuron.2004.12.009

Chen, A. L., Riley, D. E., King, S. A., Joshi, A. C., Serra, A., Liao, K., . . . Leigh, R. J. (2010). The Disturbance of Gaze in Progressive Supranuclear Palsy: Implications for Pathogenesis. *Frontiers in Neurology, 1*, 147. doi: 10.3389/fneur.2010.00147

Chun, M. M., & Wolfe, J. M. (1996). Just say no: how are visual searches terminated when there is no target present? *Cogn Psychol, 30*(1), 39-78. doi: 10.1006/cogp.1996.0002

Corbetta, M., Akbudak, E., Conturo, T. E., Snyder, A. Z., Ollinger, J. M., Drury, H. A., . . . Shulman, G. L. (1998). A common network of functional areas for attention and eye movements. *Neuron, 21*(4), 761-773.

Corbetta, M., & Shulman, G. L. (2002). Control of Goal-Directed and Stimulus-Driven Attention in the Brain. *Nature Neuroscience Reviews, 3*, 201-215.

Cowey, A., Alexander, I., & Stoerig, P. (2011). Transneuronal retrograde degeneration of retinal ganglion cells and optic tract in hemianopic monkeys and humans. *Brain, 134*, 2149-2157. doi: 10.1093/brain/awr125

Craighero, L., Carta, A., & Fadiga, L. (2001). Peripheral oculomotor palsy affects orienting of visuospatial attention. *Neuroreport, 12*(15), 3283-3286.

Craighero, L., Nascimben, M., & Fadiga, L. (2004). Eye position affects orienting of visuospatial attention. *Current Biology, 14*(4), 331-333.

de Haan, B., Morgan, P. S., & Rorden, C. (2008). Covert orienting of attention and overt eye movements activate identical brain regions. *Brain Research, 1204*, 102-111. doi: 10.1016/j.brainres.2008.01.105

Desimone, R. (1998). Visual attention mediated by biased competition in extrastriate visual cortex. *Philosophical Transactions of the Royal Society of London Series B-Biological Sciences, 353*(1373), 1245-1255.

Deubel, H., & Schneider, W. X. (1996). Saccade target selection and object recognition: Evidence for a common attentional mechanism. *Vision Research, 36*(12), 1827-1837.

Dickson, D. W., Ahmed, Z., Algom, A. A., Tsuboi, Y., & Josephs, K. A. (2010). Neuropathology of variants of progressive supranuclear palsy. *Curr Opin Neurol, 23*(4), 394-400. doi: 10.1097/WCO.0b013e32833be924

Dinkin, M. (2017). Trans-synaptic Retrograde Degeneration in the Human Visual System: Slow, Silent, and Real. *Current Neurology and Neuroscience Reports, 17*(2), 15. doi: 10.1007/s11910-017-0725-2

Fecteau, J. H., & Munoz, D. P. (2006). Salience, relevance, and firing: a priority map for target selection. *Trends in Cognitive Sciences, 10*(8), 382-390.

Fierro, B., Brighina, F., Oliveri, M., Piazza, A., La Bua, V., Buffa, D., & Bisiach, E. (2000). Contralateral neglect induced by right posterior parietal rTMS in healthy subjects. *Neuroreport, 11*(7), 1519-1521.

Gabay, S., Henik, A., & Gradstein, L. (2010). Ocular motor ability and covert attention in patients with Duane Retraction Syndrome. *Neuropsychologia, 48*(10), 3102-3109.

Gerstenecker, A., Mast, B., Duff, K., Ferman, T. J., & Litvan, I. (2013). Executive dysfunction is the primary cognitive impairment in progressive supranuclear palsy. *Arch Clin Neuropsychol, 28*(2), 104-113. doi: 10.1093/arclin/acs098

Ghosh, B. C. P., Calder, A. J., Peers, P. V., Lawrence, A. D., Acosta-Cabronero, J., Pereira, J. M., . . . Rowe, J. B. (2012). Social cognitive deficits and their neural correlates in progressive supranuclear palsy. *Brain, 135*, 2089-2102. doi: 10.1093/brain/aws128

Glasmacher, S. A., Leigh, P. N., & Saha, R. A. (2017). Predictors of survival in progressive supranuclear palsy and multiple system atrophy: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry, 88*(5), 402-411. doi: 10.1136/jnnp-2016-314956

Golbe, L. I. (2014). Progressive supranuclear palsy. *Semin Neurol, 34*(2), 151-159. doi: 10.1055/s-0034-1381736

Goldberg, M. E., Bisley, J., Powell, K. D., Gottlieb, J., & Kusunoki, M. (2002). The role of the lateral intraparietal area of the monkey in the generation of saccades and visuospatial attention *Neurobiology of Eye Movements: From Molecules to Behavior* (Vol. 956, pp. 205-215).

Grosbras, M.-H., & Paus, T. (2002). Transcranial Magnetic Stimulation of the Human Frontal Eye Field: Effects on Visual Perception and Attention. *Journal of Cognitive Neuroscience, 14*(7), 1109-1120.

Hilchey, M. D., Klein, R. M., & Satel, J. (2014). Returning to "Inhibition of Return" by Dissociating Long-Term Oculomotor IOR From Short-Term Sensory Adaptation and Other Nonoculomotor "Inhibitory" Cueing Effects. *Journal of Experimental Psychology-Human Perception and Performance, 40*(4), 1603-1616. doi: 10.1037/a0036859

Hillyard, S. A., Vogel, E. K., & Luck, S. J. (1998). Sensory gain control (amplification) as a mechanism of selective attention: electrophysiological and neuroimaging evidence. *Philosophical Transactions of the Royal Society of London B: Biological Sciences, 353*(1373), 1257-1270. doi: 10.1098/rstb.1998.0281

Höglinger, G. U., Respondek, G., Stamelou, M., Kurz, C., Josephs, K. A., Lang, A. E., . . . for the Movement Disorder Society–endorsed, P. S. P. S. G. (2017). Clinical diagnosis of progressive supranuclear palsy: The movement disorder society criteria. *Movement Disorders*, n/a-n/a. doi: 10.1002/mds.26987

Ikkai, A., & Curtis, C. E. (2011). Common neural mechanisms supporting spatial working memory, attention and motor intention. *Neuropsychologia, 49*(6), 1428-1434.

Jackson, S. R., Newport, R., Osborne, F., Wakely, R., Smith, D. T., & Walsh, V. (2005). Saccade-contingent spatial and temporal errors are absent for saccadic head movements. *Cortex, 41*(2), 205-212.

Kimura, D., Barnett, H. J. M., & Burkhart, G. (1981). The psychological test pattern in progressive supranuclear palsy. *Neuropsychologia, 19*(2), 301-306. doi: http://dx.doi.org/10.1016/0028-3932(81)90113-5

Kisvarday, Z. F., Cowey, A., Stoerig, P., & Somogyi, P. (1991). DIRECT AND INDIRECT RETINAL INPUT INTO DEGENERATED DORSAL LATERAL GENICULATE-NUCLEUS AFTER STRIATE CORTICAL REMOVAL IN MONKEY - IMPLICATIONS FOR RESIDUAL VISION. *Experimental Brain Research, 86*(2), 271-292.

Klein, R. M. (2000). Inhibition of return. *Trends in Cognitive Sciences, 4*(4), 138-147.

Lane, A. R., Smith, D. T., Ellison, A., & Schenk, T. (2010). Visual exploration training is no better than attention training for treating hemianopia. *Brain, 133*(6), 1717-1728. doi: 10.1093/brain/awq088

Lane, A. R., Smith, D. T., Schenk, T., & Ellison, A. (2012a). The involvement of posterior parietal cortex and frontal eye fields in spatially primed visual search. *Brain Stimulation, 5*(1), 11-17.

Lane, A. R., Smith, D. T., Schenk, T., & Ellison, A. (2012b). The Involvement of Posterior Parietal Cortex in Feature and Conjunction Visuomotor Search. *Journal of Cognitive Neuroscience, 23*(8), 1964-1972. doi: 10.1162/jocn.2010.21576

Litvan, I., Bhatia, K. P., Burn, D. J., Goetz, C. G., Lang, A. E., McKeith, I., . . . Wenning, G. K. (2003). Movement Disorders Society Scientific Issues Committee report: SIC Task Force appraisal of clinical diagnostic criteria for Parkinsonian disorders. *Mov Disord, 18*(5), 467-486. doi: 10.1002/mds.10459

Luck, S. J., Chelazzi, L., Hillyard, S. A., & Desimone, R. (1997). Neural mechanisms of spatial selective attention in areas V1, V2, and V4 of macaque visual cortex. *Journal of Neurophysiology, 77*(1), 24-42.

Michalczyk, Ł., Paszulewicz, J., Bielas, J., & Wolski, P. (2018). Is saccade preparation required for inhibition of return (IOR)? *Neuroscience Letters, 665*, 13-17. doi: https://doi.org/10.1016/j.neulet.2017.11.035

Monza, D. D., Soliveri, P. P., Radice, D. D., & et al. (1998). Cognitive dysfunction and impaired organization of complex motility in degenerative parkinsonian syndromes. *Archives of Neurology, 55*(3), 372-378. doi: 10.1001/archneur.55.3.372

Morgan, E. J., Ball, K., & Smith, D. T. (2014). The role of the oculomotor system in covert social attention. *Attention Perception & Psychophysics, 76*(5), 1265-1270. doi: 10.3758/s13414-014-0716-1

Muggleton, N. G., Juan, C. H., Cowey, A., & Walsh, V. (2003). Human frontal eye fields and visual search. *Journal of Neurophysiology, 89*(6), 3340-3343.

Muller, H. J., & Rabbitt, P. M. A. (1989). Reflexive and Voluntary Orienting of Visual-Attention - Time Course of Activation and Resistance to Interruption. *Journal of Experimental Psychology-Human Perception and Performance, 15*(2), 315-330.

Munoz, D. P., & Everling, S. (2004). Look away: The anti-saccade task and the voluntary control of eye movement. *Nature Reviews Neuroscience, 5*(3), 218-228.

Nath, U., Ben-Shlomo, Y., Thomson, R. G., Morris, H. R., Wood, N. W., Lees, A. J., & Burn, D. J. (2001). The prevalence of progressive supranuclear palsy (Steele–Richardson–Olszewski syndrome) in the UK. *Brain, 124*(7), 1438-1449. doi: 10.1093/brain/124.7.1438

Nobre, A. C., Gitelman, D. R., Dias, E. C., & Mesulam, M. M. (2000). Covert visual spatial orienting and saccades: Overlapping neural systems. *NeuroImage, 11*(3), 210-216.

Pearson, D. G., Ball, K., & Smith, D. T. (2014). Oculomotor preparation as a rehearsal mechanism in spatial working memory. *Cognition, 132*(3), 416-428. doi: 10.1016/j.cognition.2014.05.006

Pinching, A. J., & Powell, T. P. S. (1971). ULTRASTRUCTURAL FEATURES OF TRANSNEURONAL CELL DEGENERATION IN OLFACTORY SYSTEM. *Journal of Cell Science, 8*(1), 253-&.

Posner, M. I. (1978). *Chronometric Explorations of Mind*. Hillsdale, New Jersey: Lawrence Erlbaum Associates.

Posner, M. I. (1980). Orienting of Attention. *Quarterly Journal of Experimental Psychology, 32*(FEB), 3-25.

Posner, M. I., & Cohen, Y. (1984). Components of Visual Orienting. In H. Bouma & D. Bouwhuis (Eds.), *Attention and Performance X* (pp. 531-556). London: Erlbaum Associates.

Posner, M. I., Cohen, Y., & Rafal, R. D. (1982). Neural Systems Control of Spatial Orienting. *Philosophical Transactions of the Royal Society of London Series B-Biological Sciences, 298*(1089), 187-198.

Posner, M. I., Rafal, R. D., Choate, L. S., & Vaughan, J. (1985). Inhibition of Return - Neural Basis and Function. *Cognitive Neuropsychology, 2*(3), 211-228.

Rafal, R. D., Posner, M. I., Friedman, J. H., Inhoff, A. W., & Bernstein, E. (1988). Orienting of Visual-Attention in Progressive Supranuclear Palsy. *Brain, 111*, 267-280.

Ristic, J., Friesen, C. K., & Kingstone, A. (2002). Are eyes special? It depends on how you look at it. *Psychonomic Bulletin & Review, 9*(3), 507-513. doi: 10.3758/bf03196306

Rizzolatti, G., Riggio, L., & Sheliga, B. M. (1994). Space and Selective Attention *Attention and Performance Xv* (Vol. 15, pp. 231-265).

Robbins, T. W., James, M., Owen, A. M., Lange, K. W., Lees, A. J., Leigh, P. N., . . . Summers, B. A. (1994). Cognitive deficits in progressive supranuclear palsy, Parkinson's disease, and multiple system atrophy in tests sensitive to frontal lobe dysfunction. *Journal of Neurology, Neurosurgery, and Psychiatry, 57*(1), 79-88.

Schall, J. D., & Cohen, J. Y. (2011). The neural basis of saccade target selection. In S. P. Liversedge, I. Gilchrist & S. Everling (Eds.), *The Oxford Handbook of Eye Movements* (pp. 357-381): Oxford.

Schrag, A., Ben-Shlomo, Y., & Quinn, N. P. (1999). Prevalence of progressive supranuclear palsy and multiple system atrophy: a cross-sectional study. *Lancet, 354*(9192), 1771-1775.

Shepherd, M., Findlay, J. M., & Hockey, R. J. (1986). The Relationship between Eye-Movements and Spatial Attention. *Quarterly Journal of Experimental Psychology Section a-Human Experimental Psychology, 38*(3), 475-491.

Sigurdsson, E. M. (2016). Tau Immunotherapy. *Neuro-degenerative diseases, 16*(0), 34-38. doi: 10.1159/000440842

Smith, D. T., & Archibald, N. (2018). Spatial Working Memory in Progressive Supranuclear Palsy. *Cortex*. doi: https://doi.org/10.1016/j.cortex.2018.07.004

Smith, D. T., Ball, K., & Ellison, A. (2014). Covert visual search within and beyond the effective oculomotor range. *Vision Research, 95*, 11-17. doi: 10.1016/j.visres.2013.12.003

Smith, D. T., Ball, K., Ellison, A., & Schenk, T. (2010). Deficits of reflexive attention induced by abduction of the eye. *Neuropsychologia, 48*, 1269-1276.

Smith, D. T., Jackson, S. R., & Rorden, C. (2005). Transcranial magnetic stimulation of the left human frontal eye fields eliminates the cost of invalid endogenous cues. *Neuropsychologia, 43*(9), 1288-1296.

Smith, D. T., Jackson, S. R., & Rorden, C. (2009a). An intact eye-movement system is not required to generate Inhibition of Return. *Journal of Neuropsychology*(3), 267-271.

Smith, D. T., Jackson, S. R., & Rorden, C. (2009b). Repetitive TMS over frontal eye fields disrupts visually cued auditory attention. *Brain Stimulation, 2*, 81-87.

Smith, D. T., Rorden, C., & Jackson, S. R. (2004). Exogenous orienting of attention depends upon the ability to execute eye movements. *Current Biology, 14*(9), 792-795.

Smith, D. T., Rorden, C., & Schenk, T. (2012). Saccade preparation is required for exogenous attention but not endogenous attention or IOR. *Journal of Experimental Psychology-Human Perception and Performance, 36*(6), 1438-1447. doi: 10.1037/a0027794

Smith, D. T., & Schenk, T. (2012). The Premotor theory of attention: Time to move on? *Neuropsychologia, 50*(6), 1104-1114.

Soliveri, P., Monza, D., Paridi, D., Carella, F., Genitrini, S., Testa, D., & Girotti, F. (2000). Neuropsychological follow up in patients with Parkinson's disease, striatonigral degeneration-type multisystem atrophy, and progressive supranuclear palsy. *Journal of Neurology Neurosurgery and Psychiatry, 69*(3), 313-318. doi: 10.1136/jnnp.69.3.313

Sparks, D. L., & Mays, L. E. (1990). Signal transformations required for the generation of saccadic eye movements. *Annual Review of Neuroscience, 13*, 309-336.

Steele, J. C., Richardson, J. C., & Olszewski, J. (1964). PROGRESSIVE SUPRANUCLEAR PALSY. A HETEROGENEOUS DEGENERATION INVOLVING THE BRAIN STEM, BASAL GANGLIA AND CEREBELLUM WITH VERTICAL GAZE AND PSEUDOBULBAR PALSY, NUCHAL DYSTONIA AND DEMENTIA. *Arch Neurol, 10*, 333-359.

Thomas, N. W., & Pare, M. (2007). Temporal processing of saccade targets in parietal cortex area LIP during visual search. *J Neurophysiol, 97*(1), 942-947. doi: 10.1152/jn.00413.2006

Tipples, J. (2002). Eye gaze is not unique: Automatic orienting in response to uninformative arrows. *Psychonomic Bulletin & Review, 9*(2), 314-318.

White, B. J., & Munoz, D. P. (2011). The Superior Colliculus. In S. P. Liversedge, I. Gilchrist & S. Everling (Eds.), *The Oxford Handbook of Eye Movements* (pp. 195-215). Oxford: Oxford University Press.

Williams, D. R., de Silva, R., Paviour, D. C., Pittman, A., Watt, H. C., Kilford, L., . . . Lees, A. J. (2005). Characteristics of two distinct clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson's syndrome and PSP-parkinsonism. *Brain, 128*(Pt 6), 1247-1258. doi: 10.1093/brain/awh488

Wolfe, J. M. (1994). Guided Search 2.0 A revised model of visual search. *Psychonomic Bulletin & Review, 1*(2), 202-238. doi: 10.3758/bf03200774

Wolfe, J. M. (1998). Visual Search. In H. Pashler (Ed.), *Attention* (pp. 13-56). Hove, UK: Psychology Press.

Wolfe, J. M. (2003). Moving towards solutions to some enduring controversies in visual search. *Trends in Cognitive Sciences, 7*(2), 70-76.

Yeshurun, Y., & Carrasco, M. (1998). Attention improves or impairs visual performance by enhancing spatial resolution. *Nature, 396*(6706), 72-75.

Yoshida, K., Hata, Y., Kinoshita, K., Takashima, S., Tanaka, K., & Nishida, N. (2017). Incipient progressive supranuclear palsy is more common than expected and may comprise clinicopathological subtypes: a forensic autopsy series. *133*(5), 809-823. doi: 10.1007/s00401-016-1665-7

Zangemeister, W. H., Canavan, A. G. M., & Hoemberg, V. (1995). Frontal and Parietal Transcranial Magnetic Stimulation (TMS) Disturbs Programming of Saccadic Eye-Movements. *Journal of the Neurological Sciences, 133*(1-2), 42-52.

Zhang, J., Rittman, T., Nombela, C., Fois, A., Coyle-Gilchrist, I., Barker, R. A., . . . Rowe, J. B. (2016). Different decision deficits impair response inhibition in progressive supranuclear palsy and Parkinson’s disease. *Brain, 139*(1), 161-173. doi: 10.1093/brain/awv331